EXHIBIT 1, PAGE 1

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证　　明

本证明之附件是向本局提交的下列专利申请副本

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发明创造名称：　合成多奈哌齐及其衍生物的新方法

申　请　人：　天津和美生物技术有限公司

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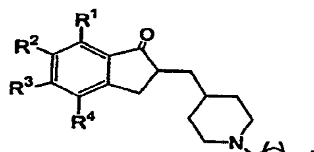
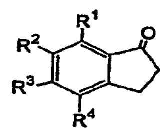
国家知识产权局局长　王景川

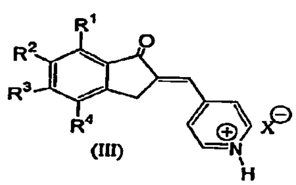
2004 年 11 月 8 日

权利要求书

1. 本发明涉及制备式（I）所示的多奈哌齐及其衍生物的新方法，其中 R^1、R^2、R^3、R^4 分别表示为 H、F、C_{1-4} 烷基或 C_{1-4} 烷氧基，R^5 表示苯基或取代的苯基，n 为 0、1 或 2，其特征为所述的方法包括下列反应步骤：
   A. 4一吡啶甲醛与式（II）所示的化合物在强酸 HX 作用下反应生成式（III）所示的化合物。
   B. 式（III）所示的化合物经催化氢化得到式（IV）所示的化合物。
   C. 式（IV）所示的化合物经烷基化反应得到式（I）所示的化合物。


(I)


(II)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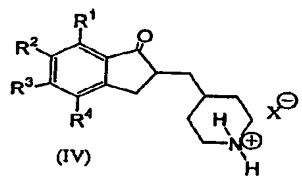
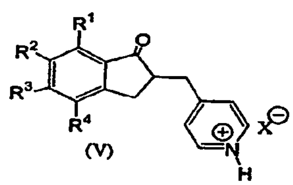

(IV)


(V)

2. 权利要求 1 中制备式（I）所示化合物的新方法，其中 R^1、R^2、R^3、R^4 分别表示为 H、F、C_{1-4} 烷基或 C_{1-4} 烷氧基，R^5 表示苯基或取代的苯基，n 为 0、1 或 2，Y 为 Cl、Br 或 I，其特征为由式（IV）所示化合物与卤代烃 $Y\text{-}(CH_2)_{n+1}R^5$ 在碱作用下反应得到式（I）所示的化合物。
3. 权利要求 1 中制备式（I）所示化合物的新方法，其中 R^1、R^2、R^3、R^4 分别表示为 H、F、C_{1-4} 烷基或 C_{1-4} 烷氧基，R^5 表示苯基或取代的苯基，n 为 0、1 或 2，其特征为式（IV）所示的化合物与 $OHC\text{-}(CH_2)_nR^5$ 在还原条件下反应

得到式（I）所示的化合物。

4. 权利要求 1 中制备式（IV）所示化合物的新方法，其中 R^1、R^2、R^3、R^4 分别表示为 H、F、C_{1-4} 烷基或 C_{1-4} 烷氧基，HX 代表烷基磺酸、苯磺酸或取代的苯磺酸、盐酸、硫酸或磷酸，其特征为式（III）所示的化合物经催化氢化反应得到式（IV）所示的化合物。

5. 权利要求 1 中制备式（IV）所示化合物的新方法，其中 R^1、R^2、R^3、R^4 分别表示为 H、F、C_{1-4} 烷基或 C_{1-4} 烷氧基，HX 代表强酸，其特征为式（V）所示的化合物经催化氢化反应得到式（IV）所示的化合物。

6. 权利要求 1 中制备式（III）所示化合物的新方法，其中 R^1、R^2、R^3、R^4 分别表示为 H、F、C_{1-4} 烷基或 C_{1-4} 烷氧基，HX 代表强酸，其特征为式（II）所示的化合物与 4—吡啶甲醛在 HX 作用下反应生成式（III）所示的化合物。

7. 权利要求 1、2 和 3 中制备式（I）所示化合物的新方法，其特征为 R^1、R^4 代表 H，R^2、R^3 代表甲氧基，R^5 表示苯基、3-氟苯基，n 代表 0，HX 代表甲磺酸、苯磺酸、对甲苯磺酸，Y 为 Cl、Br 或 I。

8. 权利要求 1、4 和 5 中制备式（IV）所示化合物的新方法，其特征为 R^1、R^4 代表 H，R^2、R^3 代表甲氧基，HX 代表甲磺酸、苯磺酸、对甲苯磺酸。

9. 权利要求 1、4 和 5 中制备式（IV）所示的化合物的新方法，其特征为式（III）和式（V）所示的化合物经催化氢化得到式（IV）所示的化合物时所使用的催化剂为钯、铂、铑、镍、钌或它们的氧化物或盐。

10. 权利要求 1 和 6 中制备式（III）所示化合物的新方法，其特征为 R^1、R^4 代表 H，R^2、R^3 代表甲氧基，HX 代表甲磺酸、苯磺酸、对甲苯磺酸。

6

合成多奈哌齐及其衍生物的新方法

一、技术领域

本发明涉及制备多奈哌齐 (Donepezil) 及其衍生物的新方法。

二、技术背景

多奈哌齐为选择性好，生物利用度高，活性高的新一代可逆性乙酰胆碱脂酶抑制剂。它可选择性作用于脑中枢乙酰胆碱脂酶的抑制，而对周边组织如心肌及血红细胞的乙酰胆碱脂酶作用弱。此外，它的生物利用度高、半衰期长，因而用药方便，且无肝毒性，病人耐受性极好。由于多奈哌齐对老年痴呆症(AD)疗效显著，其市场规模越来越大。

多奈哌齐及其衍生物的合成因而成为热点，最早的合成方法是由日本 Eisai 医药公司报道（图 1，US Patent No. 5100901)，总收率不到 20%：

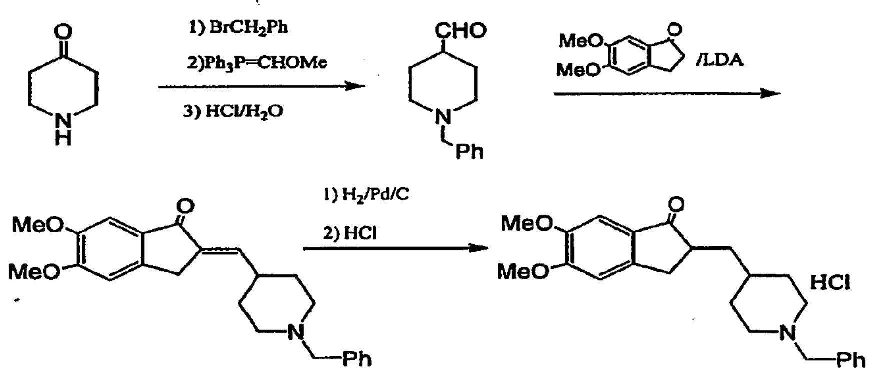


图 1

随后，EP535496 报道了一条简洁的合成路线 （图 2)，然而，德国 Bayer 公司报道该合成路线的第一步反应副产物较多，须柱层析分离纯化。我们重复该步反应时，发现同样的问题，并发现该合成工艺重复性较差。 这样，一方面，大大增加了工艺难度，另一方面，大大增加了生产成本。同时，该步反应的收率较低，使该合成工艺的总收率仅有 29% （见图 2)。可预见该工艺路线工业化生产

难度较大。EP535496 并未见后续专利申报。

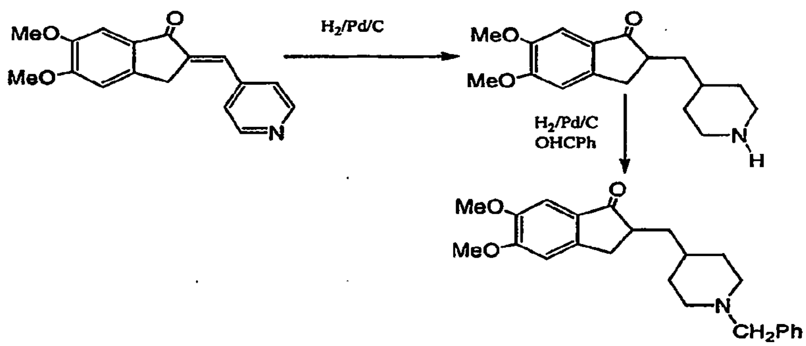


图 2

德国Bayer公司报道了一条二步反应的合成工艺路线（见图3，U. S. Patent No. 5606064）：

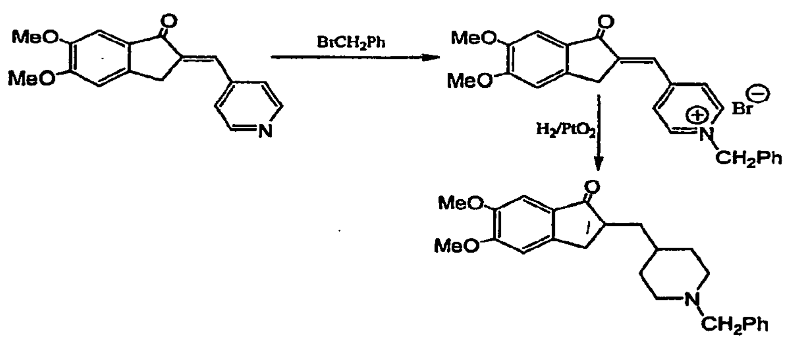


图 3

该路线报道的总收率为 53%，然而当日本 Eisai 药物公司的科学家重复该路线时，他们发现该路线中最关键的第二步收率仅有 38%（请参考 US Patent No. 6252081），因而，该合成工艺路线能得到的总收率不高于 27%。

日本 Eisai 医药公司最近推出了另一条改良工艺路线（图 4，US Patent No. 6252081）。该路线每步均可由重结晶提纯，且其最关键的最后一步收率很高，副产物很少，因而适合工业化生产，最高的总收率可达 69%。该工艺是目前报道的最佳工艺，然而，该合成工艺两步反应中用到 NaH，一步反应用到高浓度 NaOH 水溶液，两步反应需绝对无水条件，因而工艺条件要求高，工艺操作较复杂，反

应溶剂无水要求高，工艺设备无水条件、耐高浓碱条件要求高，设备投资大，因而生产成本较高。

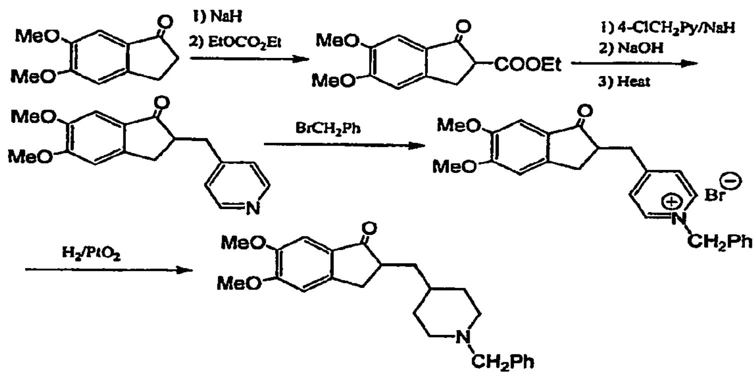


图 4

此外，Finetech 公司发展了两条全新的合成路线（图 5 和图 6，US Patent No. 6252081），其中图 5 所示的工艺无收率报道，且多步反应必须经柱层析分离纯化而使该合成工艺路线工业化价值较低：

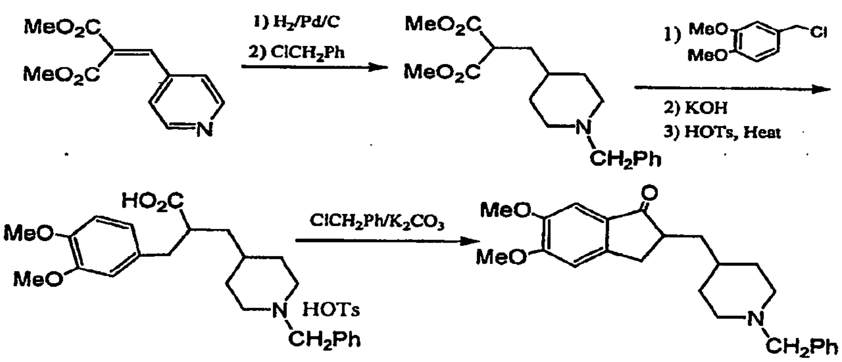


图 5

图 6 所示的第二条工艺路线虽然步骤多，各步反应可用蒸馏或重结晶的方法纯化而不须经柱层析分离纯化，使该合成工艺路线工业化价值较高。据称该合成工艺路线已经在中试规模试验成功。但该工艺路线各步反应工艺操作较复杂，多步反应用到强酸、高腐蚀性试剂，三废多，该工艺最大的缺点是反应步骤多，尽管每步反应收率均高，但总收率仅有 19.3%（见图 6），因而大大地限制了它

的工业化价值。

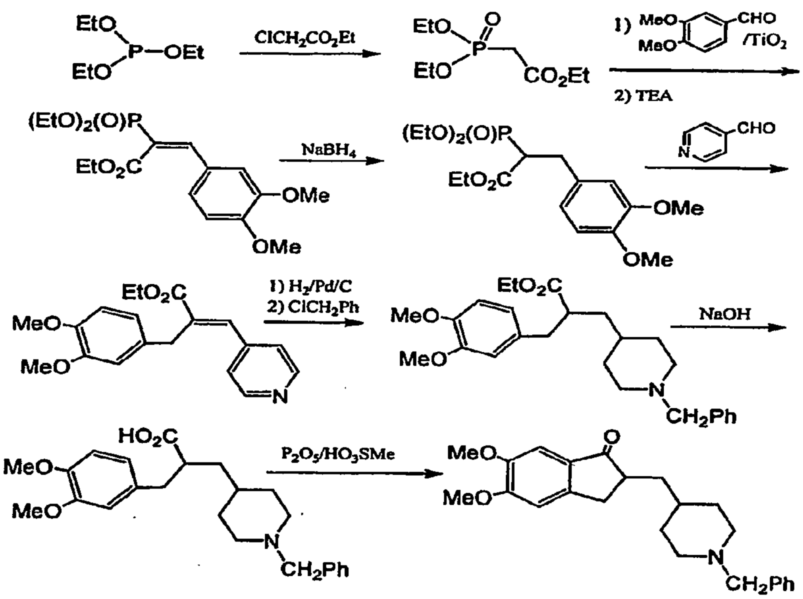


图 6

综上所述，多奈哌齐的合成报道有上述六条工艺路线，其中图 1 所示工艺已工业化生产，图 4 和图 6 所示路线已达到中试工艺规模，而图 2 所示工艺路线从申报欧洲专利至今未见后续报道，图 3 所示路线未见中试成功报道。从合成路线上分析，恰恰是图 2 和图 3 所示工艺路线最短。

从我们重复图 2 所示合成路线的结果来看，主要是由于 2－（4－吡啶亚甲基）-5，6－二甲氧基－1－茚酮为一大共轭体系，要用催化氢化的条件同时氢化双键和吡啶环比较困难。如果升高催化氢化温度，则易把羰基一并还原成羟基，从而为纯化带来困难，经柱层析纯化后的产率低于 40%。而图 3 所示的合成路线的难度也在催化氢化这一步，尽管 N-苯甲基化后生成了吡啶季铵盐而大大活化了吡啶环，但苯甲基也较易在该条件下氢解掉。日本 Eisai 公司的科学家和我们实验室重复该反应的结果均证明，该反应副产物多，不仅给纯化带来困难，同时也大大降低了收率。

克服上述困难可从两方面入手，比如日本 Eisai 公司的方法，即图 4 所示的方法，该法得到的吡啶类似物中的吡啶环不与 1-茚酮部分共轭，然后再用形成 N-

苯甲基季铵盐的方法有效地活化该吡啶环，其结果是可在非常温和的条件下催化氢化该 N一苯甲基季铵盐化的吡啶环而不影响羰基和 N-苯甲基，从而得到高收率的目标化合物。

另一个方法是用非 N-苯甲基化的方式使该吡啶环形成季铵盐而活化，从而完全避免在催化氢化该吡啶季铵盐的过程中的去苯甲基化副反应。比如 Joseph Sam 等的做法（*J. Hetercyclo. Chem* **Vol 2**, 366，见图 7），据报道该反应的收率为 100%，然而，该法不适于制备多奈哌齐。

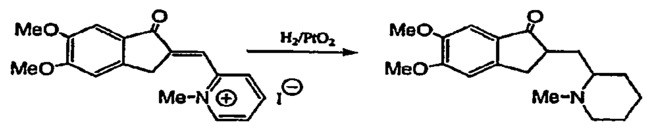


图 7

三、发明内容

综上所述，要克服图 2 和图 3 所示工艺路线的缺点关键在于活化其中的吡啶环的同时不带来新的付反应。借鉴图 7 所示反应的成功经验，我们设想用强酸使 2-（4-吡啶亚甲基）-1-茚酮衍生物中的吡啶环上的氮原子完全质子化而生成稳定的吡啶铵盐的方法来活化该吡啶环，该质子化法活化的吡啶环在催化氢化后生成的质子化哌啶环（哌啶铵盐，式 IV 所示化合物）可直接 N-苯甲基化而得到多萘哌齐或其衍生物（见图 8）。这样，不仅使式（III）所示化合物中吡啶环在温和的条件下催化氢化反应而高收率地得到式（IV）所示的化合物，而且，所得到式（IV）所示的化合物可方便地进一步烷基化成目标化合物。

相应地，本发明涉及制备式（I）所示化合物的新方法，其中 R^1、R^2、R^3 和 R^4 分别表示 H、F、C_{1-4} 烷氧基或 C_{1-4} 烷基，R^5 表示苯基或取代的苯基，n 为 0-2 的正整数，其特征为所述的方法包括图 8 所示的三步反应。

第一步反应是由式（II）所示的化合物和 4-吡啶甲醛在强酸 HX 存在下反应生成式（III）所示的化合物，其中 R^1、R^2、R^3 和 R^4 分别表示 H、F、C_{1-4} 烷氧基或 C_{1-4} 烷基，HX 为所有能使式（III）所示化合物稳定的强酸，包括但不限于烷基磺酸、苯磺酸或取代苯磺酸、对苯二磺酸、1-萘磺酸、2-萘磺酸、硫酸、磷酸、硝酸和盐酸，较合适的酸包括甲磺酸、乙磺酸、苯磺酸、对甲苯磺酸、对苯二磺酸、1-萘磺酸、2-萘磺酸、硫酸和磷酸，最合适的酸包括甲磺酸、苯磺酸、对甲

苯磺酸。

第二步反应是由式（III）所示的化合物和 H_2 在催化剂存在下反应生成式（IV）所示的化合物，其中 R^1、R^2、R^3 和 R^4 分别表示 H、F、C_{1-4} 烷氧基或 C_{1-4} 烷基，HX 为所有能使式（III）所示化合物稳定的强酸，包括但不限于烷基磺酸、苯磺酸或取代苯磺酸、对苯二磺酸、1-萘磺酸、2-萘磺酸、硫酸、磷酸、硝酸和盐酸，较合适的酸包括甲磺酸、乙磺酸、苯磺酸、对甲苯磺酸、对苯二磺酸、1-萘磺酸、2-萘磺酸、硫酸和磷酸，最合适的酸包括甲磺酸、苯磺酸、对甲苯磺酸。

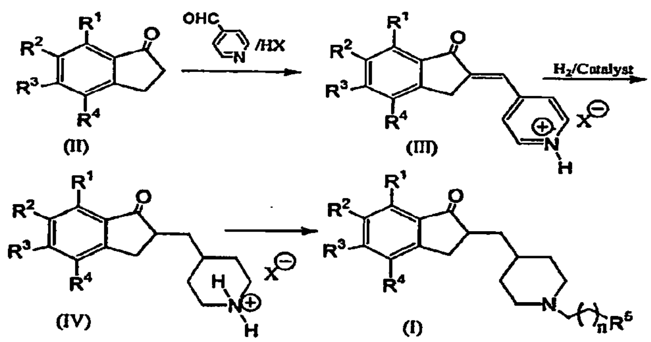
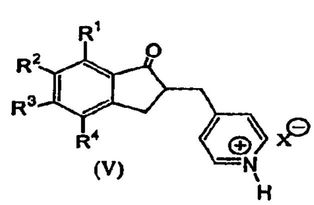


图 8

式（IV）所示化合物也可由式（V）所示化合物与氢气在催化剂存在下反应而得，其中 R^1、R^2、R^3 和 R^4 分别表示 H、F、C_{1-4} 烷氧基或 C_{1-4} 烷基，HX 可为所有能使式（V）所示化合物稳定的强酸，其中 R^1、R^2、R^3 和 R^4 分别表示 H、F、C_{1-4} 烷氧基或 C_{1-4} 烷基，HX 为所有能使式（III）所示化合物稳定的强酸，包括但不限于烷基磺酸、苯磺酸或取代苯磺酸、对苯二磺酸、1-萘磺酸、2-萘磺酸、硫酸、磷酸、硝酸和盐酸，较合适的酸包括甲磺酸、乙磺酸、苯磺酸、对甲苯磺酸、对苯二磺酸、1-萘磺酸、2-萘磺酸、硫酸和磷酸，最合适的酸包括甲磺酸、苯磺酸、对甲苯磺酸。



由式（III）或式（V）所示的化合物和 H_2 反应生成式（IV）所示的化合物所使用的催化剂可以是钯、铂、铑、镍、钌、铱等重金属及它们的氧化物或盐，较

合适的催化剂为钯碳、铂碳、二氧化铂、氯化钯、氯化铂及雷尼镍，最合适的催化剂为二氧化铂。

该步反应中适合的氢气压力为 1-100 个大气压，较合适的压力为 1-20 个大气压，最合适的压力为 1-5 个大气压。反应温度可从 0-150℃，较适宜的温度为 10-100℃，最适合的反应温度范围为从室温到 50℃。反应投料比为式(IV)所示化合物:$OHC(CH_2)_nR^5$:催化剂=1:0.5-3:0.001-0.5，较合适的投料比为式(IV)所示化合物:$OHC\text{-}(CH_2)_nR^5$:催化剂=1:0.8-1.5:0.01-0.2。反应溶剂可用水、醇类、醚类、酯类和有机酸，较合适的溶剂为水、甲醇、乙醇、丙醇、异丙醇、四氢呋喃、乙酸乙酯和乙酸，最合适的溶剂为水、甲醇、乙醇、四氢呋喃和乙酸。

第三步反应是由式（IV）所示的化合物与 $YCH_2(CH_2)_nR^5$ 在碱作用下生成式（I）所示的化合物，其中 R^1、R^2、R^3 或 R^4 分别表示 H、F、$C_{1\text{-}4}$ 烷氧基或 $C_{1\text{-}4}$ 烷基，R^5 表示苯基或取代的苯基，Y 表示 Cl、Br 或 I，n=0、1 或 2。所述的碱可以是有机碱或无机碱，较适用的碱为 K_2CO_3、Cs_2CO_3、Na_2CO_3、$KHCO_3$、$NaHCO_3$、$CaCO_3$、$Ca(OH)_2$、Li_2CO_3、K_3PO_4、Na_3PO_4、K_2HPO_4、$NaHPO_4$，最适用的碱为 K_2CO_3、Cs_2CO_3、Na_2CO_3。

该步反应合适的投料比为：式(IV)所示化合物与 $YCH_2(CH_2)_nR^5$ 的摩尔比可从 3:1 到 1:3，式(IV)所示化合物与碱的摩尔比可从 3:1 到 1:50，最适合的投料比为：式(IV)所示化物:$YCH_2(CH_2)_nR^5$:碱=1:0.8-1.5:0.8-2。

该步反应使用的溶剂可以是 N,N-二甲基甲酰胺、N,N-二甲基乙酰胺、乙腈、四氢呋喃、二氯甲烷 、三氯甲烷、1,2-二氯乙烷、1,4-二氧六环、乙酸乙酯、异丙醇、异丙醚、丙酮 、2-丁酮、六甲基磷酰胺、二甲亚砜等，较适合的溶剂为 N,N-二甲基甲酰胺、N,N-二甲基乙酰胺、乙腈、二氯甲烷、1,2-二氯乙烷、四氢呋喃、二甲亚砜、丙酮和乙酸乙酯，最适合的溶剂为 N,N-二甲基甲酰胺、N,N-二甲基乙酰胺、乙腈、二氯甲烷、1,2-二氯乙烷、四氢呋喃、二甲亚砜。反应温度可从 0℃ 到 150℃，比较合适的温度为 10-100℃，最合适的温度为室温到 50℃。

从式(IV)所示的化合物制备式(I)所示化合物的另一方法是由式(IV)所示化合物 $OHC\text{-}(CH_2)_nR^5$ 和 H_2 在催化剂作用下反应。催化剂可以是钯、铂、铑、镍、钌、铱等重金属及它们的氧化物或盐，较合适的催化剂为钯碳、铂碳、二氧化铂、氯化钯、氯化铂及雷尼镍。反应中适宜的氢气压力为 1-100 个大气压，较合适的

压力为 1-5 个大气压。可加入弱酸盐，比如醋酸钠、醋酸钾等促进反应。反应温度可从 0-150°C，较适宜的温度为 10-100°C，最适合的反应温度为室温到 50°C。反应投料比可为式(IV)所示化合物:$OHC(CH_2)_nR^5$:催化剂=1:0.5-3:0.001-0.5，较合适的投料比为式(IV)所示化合物:$OHC(CH_2)_nR^5$:催化剂=1:0.8-1.5:0.01-0.2。反应溶剂可为水、二氯甲烷、氯仿、1，4-二氧六环、醇类、醚类、酯类和有机酸，较合适的溶剂为水、甲醇、乙醇、丙醇、异丙醇、二氯甲烷、氯仿、1，4-二氧六环、四氢呋喃、乙酸乙酯和乙酸，最合适的溶剂为四氢呋喃、二氯甲烷、氯仿和 1，4-二氧六环。

从式(IV)所示化合物制备式(I)所示化合物第三种方法是由式(IV)所示化合物与 $OHC(CH_2)_nR^5$ 在还原剂作用下反应，所述的还原剂包括但不限于 $NaBH_4$、B_2H_6、$NaBH(CN)_3$、$NaBH(AcO)_3$、$Ca(BH_4)_2$，反应的投料比为式(IV)所示化合物:$OHC(CH_2)_nR^5$:还原剂=1:0.5-3:0.5-4，比较合适的投料比为式(IV)所示化合物:$OHC(CH_2)_nR^5$:还原剂=1:0.8-1.5:0.8-1.5，反应溶剂包括但不限于四氢呋喃、二氯甲烷、三氯甲烷、乙酸乙酯、1,4-二氧二环、1,2-二氯乙烷、异丙醇、异丙醚和乙酸，最合适的溶剂为四氢呋喃、二氯甲烷、三氯甲烷、乙酸乙酯、1,4-二氧二环、1,2-二氯乙烷和乙酸。反应温度可从 0-100 °C，较合适的温度是从室温到 60°C。

适于用本发明制备的式(I)所表示的化合物中适合用作活性药物成分的化合物是 R^1、R^2、R^3 和 R^4 分别表示为 H、 F、Me、OMe 或 OEt 的那些化合物，比较适合用作活性药物成分的化合物是其中 R^1、R^2 分别表示 H 或 F，R^3 和 R^4 表示 OMe 或 OEt 的那些化合物，最适合用作活性药物成分的化合物是其中 R^1、R^2 表示 H 和 R^3、R^4 表示 OMe 的那些化合物。

适于用本发明制备的式(I)所表示的化合物中适合用作活性药物成分的化合物是 R^5 表示苯基或取代苯基的那些化合物，比较适合用作活性药物成分的化合物是其中 R^5 表示苯基、3-氯苯基、3-甲基苯基、3-甲氧基苯基、2-氟苯基、3-氟苯基或 4-氟苯基的那些化合物，最适合用作活性药物成分的化合物是其中 R^5 表示苯基或 3-氟苯基的那些化合物。

适于用本发明制备的式(I)所表示的化合物中适合用作活性药物成分的化合物是 n=0、1、2 的那些化合物，比较适合用作活性药物成分的化合物是 n=0 或 1

的那些化合物，最适合用作活性药物成分的化合物是 n=0 的那些化合物。

适于用本发明制备的式(I)所表示的化合物中最适合用作活性药物成分的化合物为 R^1 和 R^4 表示为 H，R^2 和 R^3 表示 OMe，R^5 表示苯基或 3-氟苯基和 n=0 的那些化合物。

本发明所述合成工艺路线技术优越性可由实施方案中[多奈哌齐，式(II)所示化合物中 R^1、R^4 为 H，R^2、R^3 为 OCH_3，R^5 为苯基]的合成充分说明。应用本发明所述合成工艺路线，式(II)所示化合物(R^1、R^4 为 H，R^2、R^3 为 OCH_3)与 4-吡啶甲醛在对甲苯磺酸作用下，用甲苯作溶剂回流条件下反应，冷却后得到黄色晶体状的式(III)所示的化合物，收率高达 91%，纯度大于 98%，随后我们幸运的发现式(III)所示的化合物在二氧化铂催化下与一个大气压的氢气在室温下反应可获得高收率的式(IV)所示的化合物，并且后者直接以对甲苯磺酸盐的形式与苄基溴反应高税率地生成多奈哌齐，因而用本发明的合成工艺路线制备多奈哌齐总收率可达 82%。

综上所述，本发明提供了一种制备多奈哌齐及其衍生物的新方法，和现有技术相比，本发明提供的新方法具有反应步骤少、收率高、后处理纯化简便、三废少、工艺及设备要求低等优点。

本发明实施后，可大大地降低多奈哌齐的生产成本，减轻现行多奈哌齐生产工艺的环境污染的程度，因而可带来较大的社会效益和经济效益。

四、具体实施方案

实施例一

2—（4—吡啶亚甲基）—5，6—二甲氧基—1—茚酮对甲苯磺酸盐

在装备有水分分离器和电磁搅拌的圆底烧瓶中加入 0.96 克 5，6—二甲氧基—1—茚酮和 0.75 克 4—吡啶甲醛，加入 100 毫升甲苯，搅拌使固体反应物溶解后加入 0.95 克对甲苯磺酸，所得混合物搅拌回流 12 小时后冷却至室温后静置，抽滤收集所析出底黄色固体 2.141 克，收率 94%。所得固体干燥后加入 20 毫升无水乙醇，回流 30 分钟后冷却至 5°C 静置 2 小时，抽滤收集固体，滤饼用 5 毫升冷无水乙醇洗，干燥后得 1.98 克。熔点 209-212°C。^{1}H NMR (DMSO-d_6)：8.95(d, 2H, J=6.0Hz), 8.23(d, 2H, J=6.0Hz), 7.56(s, 1H), 7.48(d, 2H, J=8.0Hz), 7.27(s, 1H),

7.22(s, 1H), 7.12(d, 2H, J=8.0Hz), 4.15(s, 2H), 3.93(s, 3H), 3.85(s, 3H), 2.29(s, 3H)。

实施例二

2—（4—哌啶甲基）—5，6—二甲氧基—1—茚酮对甲苯磺酸盐

2—（4—吡啶亚甲基）—5，6—二甲氧基—1—茚酮对甲苯磺酸盐（0.402 克）溶于 30 毫升无水甲醇中，加入 33 毫克 PtO_2，在室温下，一个大气压的氢气中搅拌反应 7 小时，滤去固体，滤饼用 5 毫升无水甲醇洗，滤液旋蒸至干，加入 15 毫升的无水异丙醇，加热使之溶解，冷却至 0°C 静置过夜，抽滤得白色晶体 0.34 克，熔点 191-192°C。母液旋蒸至干浓缩后得 46 毫克固体，用液相色谱分析，其中所需产品纯度为 97%。共得 0.386 克固体，收率为 94%。 ^{1}H NMR ($DMSO-d_6$)：8.42(brs, 1H), 8.18(brs, 1H), 7.47 (d, 2H, J=8.0Hz), 7.12(d, 2H, J=8.0Hz), 7.11(s, 1H), 7.06(s, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.20-3.38 (m, 3H), 2.82-2.95(m, 2H), 2.60-2.75 (m, 2H), 2.29 (s, 3H), 1.85-1.95 (m, 1H), 1.65-1.85 (m, 3H), 1.20-1.40(m, 3H)。

实施例三

多奈哌齐的合成（方法 A）

2—（4—哌啶甲基）—5，6—二甲氧基—1—茚酮对甲苯磺酸盐（0.18 克）溶于 10mL 干燥的 N,N-二甲基甲酰胺中，一次性加入溴化苄（0.073 克）和无水碳酸钾粉末（0.3 克）。所得混合物室温下搅拌过夜。然后加入 60mL 水，所得浑浊液用乙酸乙酯萃取（4*30mL），合并乙酸乙酯萃取液用饱和 Na_2CO_3 水溶液（15mL）和饱和食盐水（15mL）洗涤，用无水硫酸镁干燥，滤去干燥剂后所得滤液旋蒸去溶剂，真空干燥后得 0.141 克产品，收率 96%。^{1}H NMR ($CDCl_3$), 7.15-7.35 (m, 5H), 7.09 (s, 1H), 6.78 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.48(s, 2H), 3.17(dd, 1H, J=8.0 Hz, J=17.6Hz), 2.82-2.92 (m, 2H), 2.58-2.74 (m, 2H), 1.80-2.03 (m, 3H), 1.57-1.76 (m, 2H), 1.40-1.56 (m, 1H), 1.18-1.40 (m, 3H)。

实施例四

2—[4—（1-间氟苯甲基哌啶）甲基]—5，6—二甲氧基—1—茚酮

用实施例三的方法由间氟苄基溴代替溴化苄制得。

实施例五

2—（4—吡啶甲基）—5，6—二甲氧基—1—茚酮

2－（4－吡啶亚甲基）－5，6－二甲氧基－1－茚酮（1.80 克）溶于 15 毫升冰醋酸中，加入 40 毫克 PtO_2，在 80°C 下，一个大气压的氢气中搅拌反应 6 小时，滤液旋蒸至干，加入 30mL 碳酸钠水溶液，所得浑浊液用氯仿萃取（5*20mL），合并氯仿萃取液用饱和食盐水洗涤，用无水硫酸镁干燥，滤去干燥剂后所得滤液旋蒸去溶剂，硅胶柱层析分离纯化（$CHCl_3/CH_3OH$=95/5 洗脱），浓缩后得 0.63 克类白色固体，收率为 35%。^{1}H NMR ($CDCl_3$)：8.53(brs, 2H), 7.15-7.25 (m, 3H), 6.82(s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.35 (dd, 1H, J=4.4, 14.0Hz), 3.12(dd, 1H, J=7.6, 16.8Hz), 2.95-3.05 (m, 1H), 2.65-2.75 (m, 2H)。

实施例六

2－（4－哌啶甲基）－5，6－二甲氧基－1－茚酮对甲苯磺酸盐

2－（4－吡啶甲基）－5，6－二甲氧基－1－茚酮（0.60 克）和对甲苯磺酸（0.36 克）溶于 30 毫升无水甲醇中，加入 60 毫克 PtO_2，在室温下、一个大气压的氢气中搅拌反应 6 小时，滤去固体，滤液旋蒸至干，真空干燥后得 1.05 克泡沫固体，收率为 100%。该品用液相色谱分析，其中所需产品纯度为 97%。

实施例七

多奈哌齐的合成（方法 B）

2－（4－哌啶甲基）－5，6－二甲氧基－1－茚酮对甲苯磺酸盐（0.22 克），醋酸钠（0.10 克）溶于 60 毫升无水甲醇中，加入 100 毫克 10% Pd/C，在反应进程 0、2、4、6 和 8 小时时各加入苯甲醛 55 毫克，在室温下和一个大气压的氢气中搅拌反应 10 小时，滤去固体，滤液旋蒸至干，加入 30mL 5% 碳酸钠水溶液，所得浑浊液用乙酸乙酯萃取（3*30mL），合并乙酸乙酯萃取液用饱和 Na_2CO_3 水溶液（15mL）和饱和食盐水（15mL）洗涤，用无水硫酸镁干燥，滤去干燥剂后所得滤液旋蒸去溶剂后得 0.67 克油，硅胶柱层析纯化后得 0.11 克，收率 62%。

METHOD FOR PRODUCING DONEPEZIL AND DERIVATIVES THEREOF

FIELD OF THE INVENTION

[0001] This invention relates to novel synthesis of Donepezil and derivatives thereof.

BACKGROUND OF THE INVENTION

[0002] Donepezil is an acetyl cholinesterase inhibitor exhibiting high selectivity, high bioavailability, and high potency. It is able to inhibit acetyl cholinesterase present in the brain while only slightly effecting acetylcholine levels present in other tissues, such as the myocardium and the erythrocytes specifically. Other advantages of using Donepezil include its persistent activity and good safety profile. In addition, patients taking Donepezil have good tolerance for the drug. Since Donepezil demonstrated good efficacy in the treatment of Alzheimer senile dementia, it is a very valuable drug with growing market share. Accordingly, Donepezil and its derivatives is a hot synthetic target.

[0003] The synthesis of Donepezil was first disclosed by Japan's Eisai Co. in the U.S. Patent No. 5,100,901 (see **Figure 1** herein), with an overall yield of less than 20%.

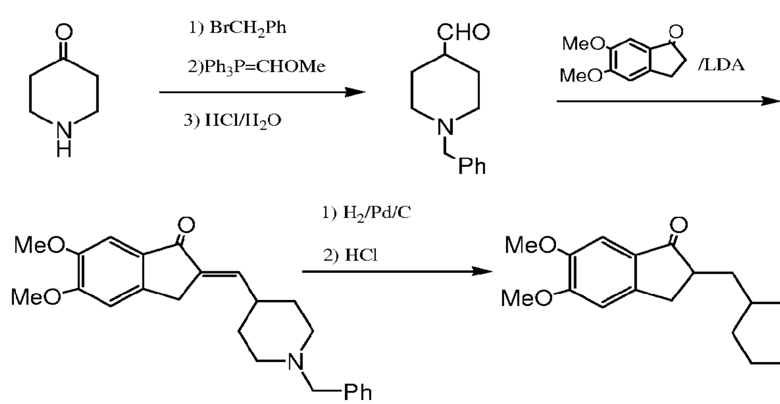


Fig. 1

[0004] EPO Patent EP 535496 then disclosed an economically viable scheme for the synthesis of Donepezil (see **Figure 2** herein). However, this synthetic route resulted in many by-products in the first step, and required complicated purification procedures, such

as column chromatography. We have found similar problems when we attempted to repeat this process. In addition, this process was difficult to reproduce. Therefore, it inevitably lead to complex purification procedure and a poor overall yield of 29 percent (see **Figure 2** herein). We predict that this process would be difficult to employ on an industrial scale. There are no continued patent applications of EP 535496 so far.

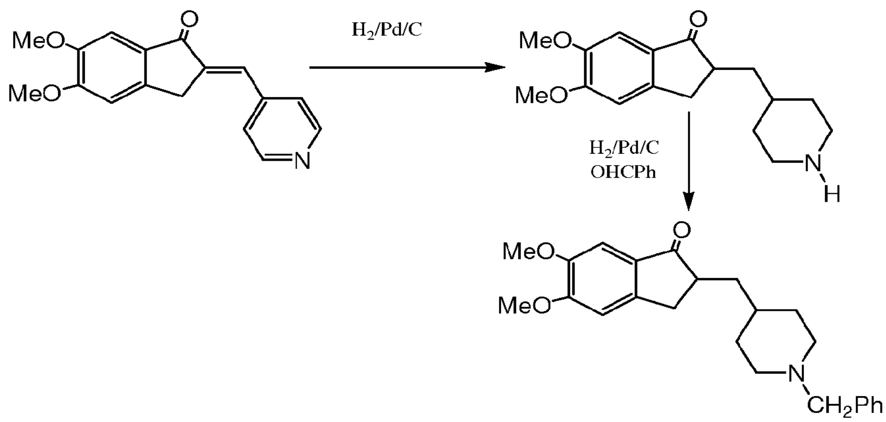


Fig. 2

[0005] The German Company Bayer disclosed yet another process for the production of Donepezil in the U.S. Patent No. 5,606,064 (see **Figure 3** herein). This process consists of 2 steps.

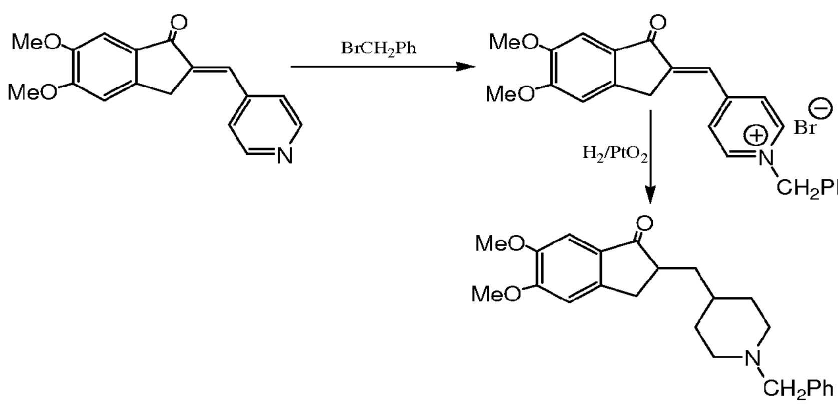


Fig. 3

[0006] The overall yield of this process is reported as 53%. However, when scientists of Eisai Co. attempted to repeat this process, they had found that the yield for the key step, step 2, was actually only 38% (U.S. Patent No. 6,252,081). Therefore, the total yield of the Bayer process could not have been more than 27% overall.

[0007] Recently, Eisai Co. disclosed in the U.S. Patent No. 6,252,081 an improved route for the preparation of Donepezil (see **Figure 4** herein). This route calls for recrystallization at each step, and the yield in the key step (last step) is high, while the by-products in that step are few. Hence, this route is the most efficient process at present, with a 69% overall yield. However, this route utilizes NaH in two steps, a high concentration NaOH solution in one step, and requires absolute dry solvents in two steps. As such, the route utilizes complicated operating parameters in each step, necessitating large investment for equipment, such as moisture proof equipment and caustic resistant equipment.

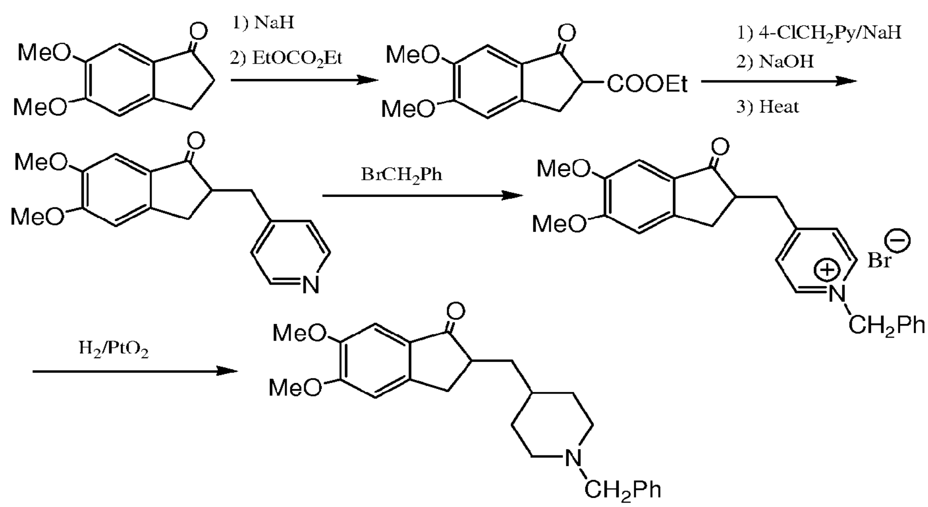


Fig. 4

[0010] Finetech also developed two novel processes (U.S. Patent No. 6,252,081; see **Figures 5 and 6** herein). The yield of the process as illustrated in Figure 5 was not disclosed, and the process required complicated purification techniques and column

chromatography in many of its steps. Therefore, this process is not deemed suitable as an industrial process.

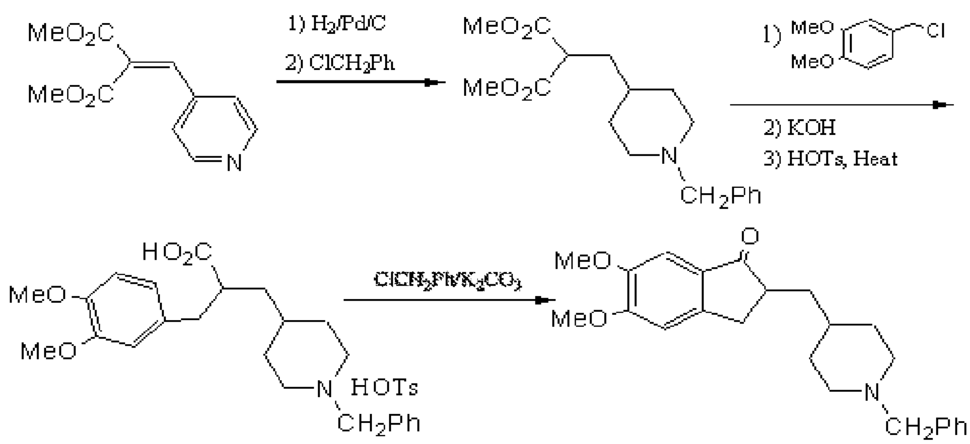


Fig. 5

[0011] Although the synthesis, disclosed in **Figure 6** herein, requires multiple steps, it employs purification by recrystallization and distillation rather than by column chromatography in each step; this renders the industrialization of the process possible. It is said that the process was successfully employed in a pilot plant. However, this process also requires complicated operating parameters in each step, and utilizes strong acid and caustic reagents in multiple steps, generating a lot of waste. This process requires many complicated steps, and although the yields of each step are high, the overall yield was a mere 19.3% (see **Figure 6** herein). For these reasons, the commercial value of the process is limited.

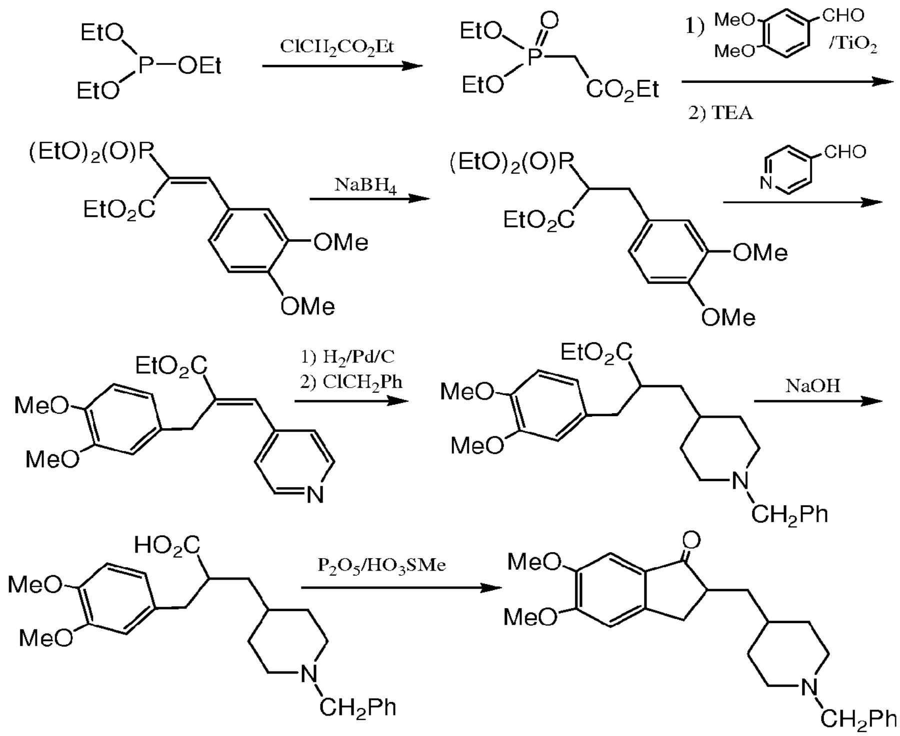


Fig. 6

[0012] In sum, there were 6 previously disclosed processes for the preparation of Donepezil and its derivatives. Wherein the process in **Figure 1** (herein) is an industrial one, processes in **Figures 4** and **6** succeeded in a pilot plant. There is no continued patent application of the process in **Figure 6** (herein) after its EP application. There is also no successful report of a pilot plant of the process in **Figure 3** (herein). The processes in **Figures 2 and 3** have the shortest synthetic route.

[0013] With respect to the results of the synthetic scheme illustrated herein in **Figure 2** which we have repeated, because the 2,3-dihydro-5, 6-dimethoxy- 2-((pyridin-4-yl)methylene)inden-1-one is a conjugated system, it is difficult to hydrogenate the pyridine ring and the carbon-carbon double bond at the same time in the presence of a catalyst. If hydrogenation is performed at an elevated temperature and pressure, the carbonyl group may also be reduced to a hydroxyl group making the purification more difficult, and yielding less than 40% of the desired material after purification by column

chromatography. Moreover, the process illustrated herein in **Figure 3** also causes trouble in the same step of catalytic hydrogenation; although the N-benzylization on the pyridine ring can form a quaternary pyridinium salt, which makes the pyridine ring more active towards hydrogenation, the benzyl group is easily broken up by hydrogenolysis under these conditions as well. The results obtained by Eisai Co. and those obtained in our laboratory show that this reaction has many by-products, which makes the purification difficult, and the yields low.

[0014] There are two methods to solve the aforesaid problems, one is to use the synthetic scheme Eisai Co. developed as shown herein in **Figure 4**: the pyridine analogues obtained from this process are not conjugated with the indanone ring; the pyridine ring can be activated through forming quaternary pyridinium salt; and as a result, the pyridine ring in the form of the N-benzyl quaternary pyridinium salt can be hydrogenated under mild reaction conditions. Consequently, the final products are obtained in higher yields.

[0015] The other method is to activate the pyridine ring by forming quaternary methyl ammonium salts rather than quaternary benzyl ammonium salts, and in this way to avoid the side reactions in the presence of a hydrogenation catalyst, as in the process disclosed by Joseph Sam (*J. Hetercyclo. Chem.* Vol. 2, 366; **Figure** 7 herein). However, although the yield of this process is said to be 100%, this process is not suitable for the preparation of Donepezil.

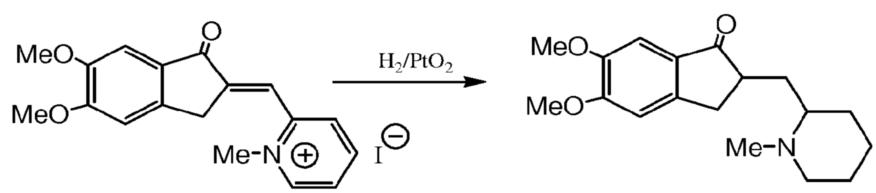


Fig. 7

[0016] SUMMARY OF THE INVENTION

[0017] To overcome the disadvantages of the synthetic schemes illustrated in **Figures 2 and 3**, we have tried to activate the pyridine ring in the absence of side reactions. Using as a guide the reaction illustrated in **Figure 7**, we attempted forming an activated

pyridinium salt via protonating the nitrogen atom of the pyridine ring of 2,3-dihydro-2-((pyridin-4-yl)methylene)inden-1-ones with a strong acid. The conjugated pyridinium ring could be easily hydrogenated in the presence of a catalyst to form a protonated piperidinium salt (represented by formula (IV) below), and to afford Donepezil and its derivatives (see **Figure 8** herein). In this way, not only the compounds of formula (IV) could be afforded in high yields through the hydrogenation of the pyridine ring of the compounds of formula (III) in the presence of a catalyst under mild reaction conditions, but also the compounds of formula (IV) could be converted to the target compounds easily by alkylation processes.

[0010] Accordingly, the invention relates to a process for producing of compounds represented by the following formula (I), wherein R^1, R^2, R^3, and R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having 1 to 4 carbon atoms; R^5 represents phenyl or substituted phenyl; and n is an integer from 0 to 2, characterized in that, the process comprises the following three reactions represented in **Figure 8** below:

[0011] Step one is the reaction of 4-pyridinecarboxaldehyde with a compound of the formula (II) to form a compound of the formula (III) in the presence of a strong acid, wherein R^1, R^2, R^3, and R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms. The term "HX" refers to a strong acid which could stabilize the compound of the formula (III), including but not limited to alkyl sulfonic acid, benzene sulfonic acid, substituted benzene sulfonic acid, terephthalic sulfonic acid, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, 1-naphthalenesulfonic acid, and 2-naphthalenesulfonic acid. Preferred acids include methyl sulfonic acid, ethyl sulfonic acid, benzene sulfonic acid, p-toluene sulfonic acid, terephthalic sulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, sulfuric acid, and phosphoric acid. More preferred acids include methyl sulfonic acid, benzene sulfonic acid and p-toluenesulfonic acid.

[0012] Second step is the reaction of a compound of the formula (III) with H_2 in the presence of a catalyst to form the compound of the formula (IV), wherein R^1, R^2, R^3, and

R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms. The term "HX" refers to a strong acid which could stabilize the compound of the formula (III), including but not limited to alkyl sulfonic acid, benzene sulfonic acid, substituted benzene sulfonic acid, terephthalic sulfonic acid, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, 1-naphthalenesulfonic acid, or 2-naphthalenesulfonic acid. Preferred acids include methyl sulfonic acid, ethyl sulfonic acid, benzene sulfonic acid, p-toluene sulfonic acid, terephthalic sulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, sulfuric acid, and phosphoric acid. More preferred acids include methyl sulfonic acid, benzene sulfonic acid, and p-toluene sulfonic acid.

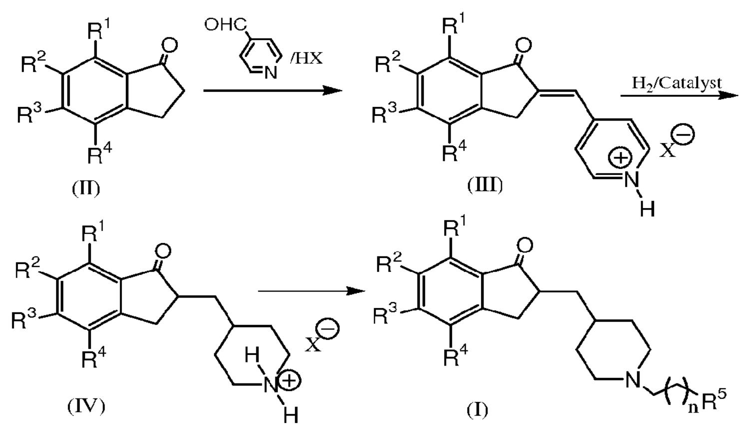
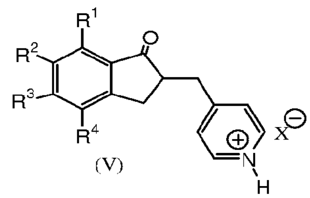


Fig. 8

[0013] A compound of the formula (IV) could be produced by the reaction of a compound of the formula (V) with H_2 in the presence of a catalyst, wherein R^1, R^2, R^3, and R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms. The term "HX" refers to a strong acid which could stabilize the compound of the formula (V) or (III), including but not limited to alkyl sulfonic acid, benzene sulfonic acid, substituted benzene sulfonic acid, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, 1-naphthalenesulfonic acid, and 2-naphthalene sulfonic acid. Preferred acids include methyl sulfonic acid, ethyl sulfonic acid, benzene sulfonic acid, p-toluene sulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic

acid, sulfuric acid, nitric acid, and phosphoric acid. More preferable acids include methyl sulfonic acid, benzene sulfonic acid, and p-toluene sulfonic acid.



(V)

[0014] Examples of catalysts used in the hydrogenation reactions in which a compound of formula (IV) is produced from a compound of formula (III) or in which a compound of formula (V) reacts with H_2 include platinum, palladium, rhodium, nickel, ruthenium, and also oxides or salts thereof. Preferred are palladium on carbon, platinum on carbon, Raney nickel, platinum dioxide, platinum chloride, and palladium chloride. More preferred is platinum dioxide.

[0015] The reaction can be carried out in a pressure range from about 1 atmosphere to about 100 atmospheres of H_2, preferably from about 1 to about 20 atmospheres, and more preferably from about 1 to about 5 atmospheres. The reaction generally is carried out in a temperature range from about 0 degrees Celsius to about +150 degrees Celsius, preferably from about +10 degrees Celsius to about +100 degrees Celsius, and more preferably from room temperature to about +50 degrees Celsius. The ratio of a reactant, for example of a compound of formula (IV) such as $OHC(CH_2)_nR_5$ to a catalyst is 1: 0.5-3: 0.001-0.5, and preferably 1: 0.8-1.5: 0.01-0.2. A suitable solvent in this reaction may be selected from, but is not limited to, water, an alcohol, an ether, an ester, or an organic acid; preferably water, methanol, ethanol, propanol, isopropanol, tetrahydrofuran, ethyl acetate, or acetic acid; and more preferably water, methanol, ethanol, tetrahydrofuran, or acetic acid.

[0016] The third step is the reaction of $Y\text{-}(CH_2)_{n+1}R^5$ with a compound of formula (IV) in the presence of a base to give a compound of formula (I), wherein R^1, R^2, R^3, and R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms; R^5 represents a phenyl or a substituted phenyl; n is an

integer from 0 to 2; and Y is a chlorine atom, a bromine atom, or an iodine atom. The base is an organic base or an inorganic base; preferably K_2CO_3, Cs_2CO_3, Na_2CO_3, $KHCO_3$, $NaHCO_3$, $CaCO_3$, $Ca(OH)_2$, Li_2CO_3, K_3PO_4, Na_3PO_4, K_2HPO_4, or Na_2HPO_4; and more preferably K_2CO_3, Cs_2CO_3 or Na_2CO_3.

[0017] The molar ratio of a compound of formula (IV) to a compound of formula $YCH_2(CH_2)_nR^5$ ranges from 1:0.3 to 1:3. The molar ratio of a compound of formula (IV) to a base ranges from 1:0.3 to 1:50. More preferably the ratio of a compound of formula (IV) to a compound of formula $YCH_2(CH_2)_nR^5$ to a base is 1 to 0.8-1.5 to 0.8-2.

[0018] Examples of solvents used in this reaction include N, N-dimethylformamide, N, N-dimethylacetamide, acetonitrile, tetrahydrofuran, dichloromethane, trichloromethane, 1,2-dichloroethane, 1,4-dioxane, ethyl acetate, isopropanol, isopropyl ether, acetone, 2-butanone, HMPA, and dimethylsulfoxide; preferably, N, N-dimethylformamide, N, N-dimethylacetamide, acetonitrile, dichloromethane, 1,2-dichloroethane, tetrahydrofuran, dimethyl sulfoxide, acetone, and ethyl acetate; and more preferably, N, N-dimethylformamide, N, N-dimethylacetamide, acetonitrile, dichloromethane, 1,2-dichloroethane, tetrahydrofuran, and dimethyl sulfoxide. The reaction is in general carried out in a temperature range from 0 degrees Celsius to +150 degrees Celsius; preferably, from 10 degrees Celsius to +100 degrees Celsius; and more preferably from room temperature to +50 degrees Celsius.

[0019] Another method for the preparation of a compound of formula (I) is the reaction of $OHC\text{-}(CH_2)_nR^5$ with a compound of formula (IV) and H_2, in the presence of a catalyst. The catalyst is platinum, palladium, nickel, rhodium, or ruthenium, or salts or oxides thereof. Preferably the catalyst is palladium on carbon, platinum on carbon, platinum dioxide, palladium chloride, platinum chloride, or Raney nickel. More preferably the catalyst is palladium on carbon. H_2 can be supplied at a pressure range from 1 to 100 atmospheres; and preferably at a pressure from 1 to 5 atmospheres. Adding a weak-acids salt such as sodium acetate, and potassium acetate will improve the reaction. The reaction is in general carried out in a temperature range from 0 degrees Celsius to +150 degrees Celsius; preferably, from 10 degrees Celsius to +100 degree Celsius; and more preferably

from room temperature to +50 degrees Celsius. The molar ratio of a compound of formula (IV) to a compound of formula $OHC(CH_2)_nR^5$ to a catalyst is 1 to 0.5-3 to 0.001-0.5. Preferably, the molar ratio of a compound of formula (IV) to a compound of formula $OHC(CH_2)_nR^5$ to a catalyst is 1 to 0.8-1.5 to 0.01-0.2. The solvent in this reaction may be selected from water, dichloromethane, chloroform, 1,4-dioxane, an alcohol, an ether, an ester, or an organic acid; preferably from, water, methanol, ethanol, propanol, isopropanol, dichloromethane, chloroform, 1,4-dioxane, tetrahydrofuran, ethyl acetate, or acetic acid; and more preferably from, tetrahydrofuran, dichloromethane, chloroform, or 1,4-dioxane.

[0020] The third method for preparation of a compound of formula (I) is the reaction of a compound of formula $OHC\text{-}(CH_2)_nR^5$ with a compound of formula (IV) and a reducing agent, wherein the reducing agent is selected from, but not limited to, $NaBH_4$, B_2H_6, $NaBH(CN)_3$, $NaBH(AcO)_3$, and $Ca(BH_4)_2$. The molar ratio of a compound of formula (IV) to a compound of formula $OHC(CH_2)_nR^5$ to a reducing agent is 1 to 0.5-3 to 0.5-4. Preferably, the molar ratio of a compound of formula (IV) to a compound of formula $OHC(CH_2)_nR^5$ to a reducing agent is 1 to 0.8-1.5 to 0.8-1.5. The solvent in this reaction is selected from, but not limited to, tetrahydrofuran, dichloromethane, trichloromethane, ethyl acetate, 1,4-dioxane, 1,2-dichloroethane, isopropanol, isopropyl ether, and acetic acid; and preferably, tetrahydrofuran dichloromethane, trichloromethane, ethyl acetate, 1,4-dioxane, 1,2-dichloroethane and acetic acid. The reaction is in general carried out in a temperature range from 0 degrees Celsius to +100 degrees Celsius; and more preferably, from room temperature to +60 degrees Celsius.

[0021] Compounds which are suitable to be used as an active pharmaceutical ingredient in therapeutic compositions and suitable to be produced by methods of this invention are compounds represented by formula (I), wherein R^1, R^2, R^3, and R^4 each independently represent H, F, Me, OMe or OEt; preferably, R^1 and R^2 each independently represent H, or F; R^3 and R^4 each independently represent OMe or OEt; more preferably, R^1 and R^2 each represent H; and R^3 and R^4 each represent OMe.

[0022] Compounds which are suitable to be used as an active pharmaceutical ingredient in therapeutic compositions and suitable to be produced by methods of this invention are compounds represented by formula (I), wherein R^5 represents phenyl or substituted phenyl; preferably, R^5 represents phenyl, 3-chloropropylphenyl, 3-bromomethylphenyl, 3-methoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, or 4-fluorophenyl; and more particularly, R^5 represents phenyl or 3-fluorophenyl.

[0023] Compounds which are suitable to be used as an active pharmaceutical ingredient in therapeutic compositions and suitable to be produced by methods of this invention are compounds represented by formula (I), wherein n is an integer from 0 to 2; preferably, n is 0 or 1; and more preferably, n is 0.

[0024] More preferably, compounds which are suitable to be used as an active pharmaceutical ingredient in therapeutic compositions and suitable to be produced by methods of this invention are compounds represented by formula (I), wherein R^1 and R^4 each represent H; R^2 and R^3 each represent OMe; R^5 represents phenyl or 3-fluorophenyl; and n is 0.

[0025] In certain embodiments, the invention shows advantages as explained in detail with reference to examples describing synthesis of Donepezil, wherein R^1 represents hydrogen, R^2 represents OMe, R^3 represents OCH_3, R^4 represents hydrogen, and R^5 represents phenyl. The addition of the 4-pyridylmethylene moiety to the compound of formula (II) (wherein R^1 represents hydrogen, R^2 represents OMe, R^3 represents OCH_3, and R^4 represents hydrogen) is described below. Specifically, the reaction of 4-pyridinecar-boxaldehyde with a compound of formula (II) in the presence of p-toluenesulfonic acid under reflux conditions in the toluene as solvent results after cooling in a brown crystalline compound of formula (III). The product is obtained in a high yield of 91%. The purity of this product is greater than 98%. In addition, we have found that compounds of formula (IV) can be obtained by reacting a compound of formula (III) with H_2 in the presence of a catalyst, such as platinum dioxide. H_2 is supplied at 1 atmosphere of pressure and room temperature. The resulted reduced p-toluene-sulfonic acid salt (IV)

is converted to Donepezil by the reaction with benzyl bromide. Therefore, the total yield of the Donepezil route according to this invention is as high as 82%.

[0026] Accordingly, the invention affords a process for the preparation of Donepezil and derivatives thereof, which compared with prior techniques, demonstrates the advantage of mild reaction conditions, easy operation and control, and little waste.

[0027] The implementation of syntheses of this invention can reduce the cost of producing Donepezil, improve product economics, and decrease pollution.

[0028] EXAMPLES

Example 1

[0029] 2,3-dihydro-5,6-dimethoxy-2-((pyridin-4-yl)methylene)inden-1-one p-toluenesulfonic acid salt

[0030] 0.96 g of 5,6-dimethoxy-1-indanone, and 0.75 g 4-pyridyl formaldehyde were added to a three-neck round bottom flask equipped with a Dean-Stark trap and an electromagnetic stirrer. 100 ml toluene was then added. Stirring continued until the reactants were dissolved. Then, 0.95 g of p-toluenesulfonic acid was added. The reaction was then carried out by refluxing for 12 hrs. After cooling, a solid was formed. The resultant solid was filtered off with suction affording 2.141 g of a yellow solid compound. The yield was 94 %. 20 mL of anhydrous ethanol were added to the product, and the slurry was brought under reflux in ethanol for 30 minutes. After cooling at 5°C for 2 hours, the resulting precipitate was filtered off with suction and after washing with 5 ml cold anhydrous ethanol and drying, 1.98 g of the title product were obtained. The melting point range was from 209-212°C. ^{1}H NMR (DMSO-d_6): 8.95 (d, 2H, J=6.0Hz), 8.23 (d, 2H, J=6.0Hz), 7.56 (s, 1H), 7.48 (d, 2H, J=8.0Hz), 7.27 (s, 1H), 7.22 (s, 1H), 7.12 (d, 2H, J=8.0Hz), 4.15 (s, 2H), 3.93 (s, 3H), 3.85 (s, 3H), 2.29 (s, 3H).

Example 2

[0031] 2,3-dihydro-5, 6-dimethoxy-2-((piperidin-4-yl)methyl)inden-1-one p-toluenesulfonic acid salt

[0032] 0.402 g of 2,3-dihydro-5,6-dimethoxy-2-((pyridin-4-yl)methylene)inden-1-one p-toluenesulfonic salt were dissolved in 30 mL of methanol and 33 milligram of PtO_2 were added. Stirring continued at room temperature, with H_2 being supplied at 1 atmosphere for 7 hours. Solids filtered off with suction and washed with 5 ml anhydrous methanol. After concentrating the filtrate solid was obtained. To the solid 15 mL of anhydrous isopropanol was added. The mixture was heated to dissolve solids and then cooled to 0°C overnight. The formed precipitate was filtered off with suction to afford 0.34 g of white crystalline solid. The melting point 191-192°C. After drying, additional 46 milligrams of solid were obtained. Liquid chromatography analysis showed product of 97% purity. A total of 0.386 g of the expected product was obtained at a yield of 94%. ^{1}H NMR (DMSO-d_6)： 8.42 (br s, 1H), 8.18 (br s, 1H), 7.47 (d, 2H, *J*=8.0Hz), 7.12 (d, 2H, *J*=8.0Hz), 7.11 (s, 1H), 7.06 (s, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.20-3.38 (m, 3H), 2.82-2.95 (m, 2H), 2.60-2.75 (m, 2H), 2.29 (s, 3H), 1.85-1.95 (m, 1H), 1.65-1.85 (m, 3H), 1.20-1.40 (m, 3H).

Example 3

[0033] Synthesis of Donepezil (Method A)

[0034] 0.18 g of 2, 3-dihydro-5, 6-dimethoxy-2-((piperidin-4-yl)methyl)inden-1-one p-toluenesulfonic acid salt were dissolved in 10 mL of dry N,N'-dimethylformamide. 0.073 g of benzyl bromide and 0.3 g of potassium carbonate were added thereto. The resulted mixture was stirred until the reaction completed. Then 60 mL of water were added and the solution was extracted with 4 x 30 mL of ethyl acetate. The extracts were combined, washed with 15 mL of Na_2CO_3 solution and with 15 mL NaCl solution, and dried over anhydrous $MgSO_4$. Drying agent was then filtered off. The solvent was removed *in vacuo* yielding 0.141 g of product, 96% yield. ^{1}H NMR ($CDCl_3$), 7.15-7.35 (m, 5H), 7.09 (s, 1H), 6.78 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.48(s, 2H), 3.17 (dd, 1H, *J*=8.0 Hz,

J=17.6Hz), 2.82-2.92 (m, 2H), 2.58-2.74 (m, 2H), 1.80-2.03 (m, 3H), 1.57-1.76 (m, 2H), 1.40-1.56 (m, 1H), 1.18-1.40 (m, 3H).

Example 4

[0035] 2-((1-(3-fluorobenzyl)piperidin-4-yl)methyl)-2,3-dihydro-5,6-dimethoxyinden-1-one, was prepared according to Example 3 by replacing benzyl bromide with m-fluorobenzyl bromide.

Example 5

[0036] 2,3-dihydro-5,6-dimethoxy-2-((pyridin-4-yl)methyl)inden-1-one

[0037] 1.80 g of 2,3-dihydro-5,6-dimethoxy-2-((pyridin-4-yl)methylene)inden-1-one and 40 milligrams of PtO_2 were added to 15 mL glacial acetic acid. The reaction mixture was stirred at 80 °C, with H_2 being supplied at 1 atmosphere for 6 hours. Solids were filtered off. The filtrate was concentrated. 30 mL of Na_2CO_3 aqueous solution were added thereto. The resulted mixture was extracted with of chloroform (5 x 20 mL). The extracts were combined, washed with brine, and dried over anhydrous $MgSO_4$. The drying agent was then filtered off. Solvent was removed *in vacuo* to give crude product. Purification of crude product by silica gel column chromatography ($CHCl_3$/CH_3OH 95/5) afforded 0.63 g of white crystalline compound. The yield was 35%. ^{1}H NMR ($CDCl_3$)： 8.53(brs, 2H), 7.15-7.25 (m, 3H), 6.82(s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.35 (dd, 1H, J=4.4, 14.0Hz), 3.12(dd, 1H, J=7.6, 16.8Hz), 2.95-3.05 (m, 1H), 2.65-2.75 (m, 2H).

Example 6

[0038] 2,3-dihydro-5,6-dimethoxy-2-((piperidin-4-yl)methyl)inden-1-one p-toluenesulfonic acid salt

[0039] 0.60 g of 2,3-dihydro-5,6-dimethoxy-2-((pyridin-4-yl)methyl)inden-1-one, and 0.36 g p-toluenesulfonic acid salt were added to 30 mL of anhydrous methanol. 60 milligrams of PtO_2 were added. The reaction mixture was stirred at room temperature, with H_2 being added at 1 atmosphere for 6 hours. Solids were filtered off. The filtrate was

concentrated and dried *in vacuo* to afford 1.05 g of foam with 100% yield. Liquid chromatography analysis of this product showed 97% purity.

Example 7

[0040] Synthesis of Donepezil (Method B)

[0041] 0.22 g of 2,3-dihydro-5,6-dimethoxy-2-((piperidin-4-yl)methyl)inden-1-one p-toluenesulfonic acid salt, and 0.10 g of sodium acetate were added to 60 mL of anhydrous methanol. 100 milligrams of 10% Pd/C were also added. The reaction mixture was stirred at room temperature with H_2 being supplied at 1 atmosphere for 10 hours. 55 milligrams of benzaldehyde were added in equal portions at 0 hrs, 2 hrs, 4 hrs, 6hrs and 8 hrs. Solids were filtered off. The filtrate was concentrated. 30 mL of 5% aqueous Na_2CO_3 solution were added, and the resulting mixture was extracted with 3 x 30 mL of ethyl acetate. The extracts were combined, washed with 15 mL of aqueous Na_2CO_3 solution and 15 mL of aqueous NaCl solution, and dried over anhydrous $MgSO_4$. After solids were filtered off, solvent was removed *in vacuo* to afford 0.67 g of product as oil. Purification on silica gel column chromatography afforded 0.11 g of title compound in 62% yield.

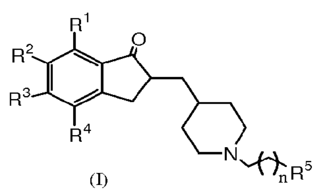
CLAIMS

1. A process for producing a Donepezil derivative of formula (I), wherein R^1, R^2, R^3, and R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms; R^5 represents a phenyl or a substituted phenyl; and n is an integer from 0 to 2, characterized in that the process comprises:

   a) a reaction of 4-pyridinecarboxaldehyde with a compound of formula (II) to form in the presence of a strong acid HX a compound of the formula (III);

   b) a catalytic hydrogenation of a compound of formula (III) or the compound of formula (V) to yield a compound of formula (IV); and

   c) an alkylation reaction of a compound of formula (IV) to yield a compound of formula (I).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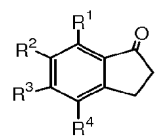
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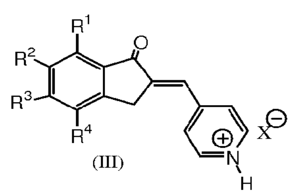
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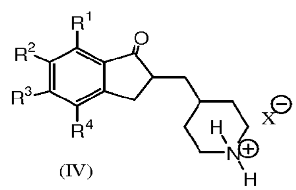
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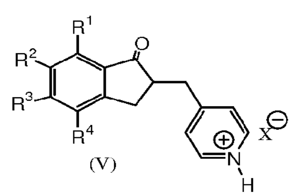
(V)

2. The process according to claim 1 for the preparation of a compound of the general formula (I), wherein R^1, R^2, R^3, and R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having 1 to 4 carbon atoms;

R^5 represents a phenyl or substituted phenyl; and n is an integer from 0 to 2, characterized in that a compound of formula (I) is produced by reacting a compound of formula Y-$(CH_2)_{n+1}R^5$ with a compound of formula (IV) in the presence of a base, wherein Y represents a chlorine atom, a bromine atom, or an iodine atom.

3. The process according to claim 1 for the preparation of a compound of the general formula (I), wherein R^1, R^2, R^3, and R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms; R^5 represents a phenyl or a substituted phenyl; and n is an integer from 0 to 2, characterized in that a compound of formula (I) is produced by reacting a compound of formula OHC-$(CH_2)_nR^5$ with a compound of formula (IV), in the presence of a reducing agent.

4. The process according to claim 1 for the preparation of a compound of the general formula (IV), wherein R^1, R^2, R^3, and R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms; HX represents an alkyl sulfonic acid, benzene sulfonic acid, a substituted benzene sulfonic acid, hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid, characterized in that a compound of formula (IV) is produced by the catalytic hydrogenation of a compound of formula (III).

5. The process according to claim 1 for the preparation of a compound of the general formula (IV), wherein R^1, R^2, R^3, and R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms; and HX represents a strong acid, characterized in that a compound of formula (IV) is produced by catalytic hydrogenation of a compound of formula (V).

6. The process according to claim 1 for the preparation of a compound of the general formula (III), wherein R^1, R^2, R^3, and R^4 each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms; and HX represents a strong acid, characterized in that 4-pyridinecarboxaldehyde reacts with a compound of formula (II) in the presence of a strong acid HX to form a compound of the formula (III).

7. The process according to any of claims 1 or 2 or 3 for the preparation of a compound of the general formula (I), characterized in that R^1 represents hydrogen; R^2 represents a methoxy; R^3 represents a methoxy; R^4 represents hydrogen; R^5 represents a phenyl or a 3-fluorophenyl; n is 0; HX represents methyl sulfonic acid, benzene sulfonic acid, or p-toluenesulfonic acid; and Y represents a chlorine, a bromine, or an iodine.

8. The process according to any of claims 1 or 4 or 5 for the preparation of a compound of the general formula (IV) wherein R^1 represents hydrogen, R^2 represents methoxy, R^3 represents methoxy, R^4 represents hydrogen, and HX represents methyl sulfonic acid, benzene sulfonic acid, or p-toluenesulfonic acid.

9. The process according to any of claims 1 or 4 or 5 for the preparation of a compound of the general formula (IV), wherein said compound of formula (IV) is produced from a compound of formula (III) and a compound of formula (V) by catalytic hydrogenation, wherein the catalyst is platinum, palladium, nickel, ruthenium, or salts or oxides thereof.

10. The process according to claims 1 or 6 for the preparation of a compound of the general formula (III), wherein R^1 represents hydrogen, R^2 represents methoxy, R^3 represents methoxy, R^4 represents hydrogen, and HX represents methyl sulfonic acid, benzene sulfonic acid, or p-toluenesulfonic acid.